Attorney Docket # 4948-2PCRCE3

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Carlos PICORNELL DARDER

Serial No.: 09/491,624

Filed: January 26, 2000

For: Oral Pharmaceutical Preparation Comprising an Antiulcer Activity Compound, and Process for its Production

Examiner: Sharmila S. Gollamudi
Group Art: 1616

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APPELLANT'S REPLY BRIEF

SIR:

This is in reply, pursuant to 37 C.F.R. §41.41. An Appeal Brief was filed on December 27, 2007. The rejected claims were reproduced in Appendix A attached to the Appeal Brief. The Examiner's Answer is dated May 29, 2008.

A Request for Oral Hearing is also enclosed with the requisite fee of $515.00 pursuant to 37 C.F.R. §41.20)(b)(3). Any additional fees or charges in connection with this application may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

REAL PARTY IN INTEREST

The assignee[1], Liconsa, Liberación Controlada de Sustancias Activas, S.A. is the real part of interest in the above-identified U.S. Patent Application.

RELATED APPEALS AND ITNERFERENCES

There are no other appeals and/or interferences related to the above-identified application at the present time.

STATUS OF THE CLAIMS

Claims 15, 16, 18-25, 30, 31, 33, 34, 36 and 39-50 were finally rejected. Claims 15, 16, 18-25, 30, 31, 33, 34, 36 and 39-50 are on appeal.

Claims 1 to 14, 17, 26 to 29, 32, 37 and 38 were cancelled without prejudice.

STATUS OF AMENDMENTS

An Amendment After Final Rejection was filed on September 27, 2007 in response to the Final Office Action. The Examiner issued an Advisory Action in reply on October 16, 2007 refusing to enter that Amendment and maintaining the rejections of July 27, 2007.

SUMMARY OF THE CLAIMED SUBJECT MATTER

Independent claim 34

Independent Claim 34 relates to a process for making an oral pharmaceutical preparation. (Specification, page 15, lines 3 to 18). The process comprises coating an inert nucleus to form a substantially non-porous layer thereon by spraying on the nucleus an aqueous or hydroalcoholic suspension solution. The sprayed solution comprises an active ingredient which active ingredient is a compound having anti-ulcer activity. (Specification, page 8, lines 15 to 21). The active ingredient is a substituted benzimidazole compound. (Specification, page 7, line 6 to line 14). The

[1] The assignee of record has changed its name to Laboratories Liconsa, S.A.

aqueous or hydroalcoholic suspension solution also comprises an alkaline reacting compound and at least one pharmaceutically acceptable excipient which can be a binder and/or a disintegrating swelling excipient. (Specification, page 11, line 1 to page 12, line 15). The active layer which is formed on the inert nucleus during the spraying is then dried to form a charged nucleus (Specification, page 16, lines 17 to 19). The charged nucleus is coated by spraying on the charged nucleus, a solution which contains an enteric coating polymer so as to form a gastro-resistant external coating on the charged nucleus. (Specification, page 16, line 10 to page 18, line 4). Each of the steps of the coating of the inert nucleus, the drying of the active layer to form the charged nucleus and the coating of the charged nucleus are performed in a Wurster-type fluidized bed coater. (Specification, page 1, lines 17 to 20).

Independent Claim 36

Independent claim 36 is drawn to a process for making an oral pharmaceutical preparation which again comprises coating an inert nucleus in a fluidized bed coater to form a substantially non-porous layer thereon by spraying on the nucleus an aqueous or hydroalcoholic suspension solution. The suspension solution includes an active ingredient, which is an anti-ulcer compound of the specified formulae, an alkaline reacting compound and a pharmaceutically acceptable excipient. The active layer that is formed on the inert nucleus is dried to form a charged nucleus in the fluid bed coater and the charged nucleus is coated in the fluid bed coater by spraying on the charged nucleus a solution containing an enteric coating polymer with at least one pharmaceutically acceptable excipient to form a gastro-resistant external coating layer thereon. (Specification, page 15, lines 3 to 18). The fluidized bed coater is Wurster-type fluidized bed coater. (Specification, page 17, lines 18 to 20).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. The rejection of claims 15, 16, 18-25, 30, 31, 33, 34, 36, 39-46 and 49 under 35 U.S.C. §103(c) as unpatentable over U.S. Patent No. 6,365,184 to Depui et al. ("Depui '184") by itself or in view of Wurster, U.S. Patent No. 2,799,241 ("Wurster").

2. The rejection of claims 15, 16, 18-25, 30, 31, 33, 34, 36, 39-46 and 49 under 35 U.S.C. §103(c) as unpatentable over U.S. Patent No. 6,132,771 to Depui et al. ("Depui '771") in view of Ohno et al., U.S. Patent No. 4,017,647 ("Ohno") or Wurster.

3. The rejection of claims 15, 16, 18-25, 30, 31, 33, 34, 36, 39-46 and 49 under 35 U.S.C. §103(a) as unpatentable over WO 96/01624 ("WO '624") in view of Ohno or Wurster.

4. The rejection of claims 47, 48 and 50 under 35 U.S.C. §103(a) as unpatentable over Depui '184 in view of Wurster in view of U.S. Patent No. 5,232,706 to Palomo Coll ("Palomo") further in view of U.S. Patent No. 5,219,870 to Kim et al. ("Kim").

5. The rejection of claims 47, 48 and 50 under 35 U.S.C. §103(a) as unpatentable over Depui '771 or WO '624 respectively, in view of Ohno or Wurster respectively, in view of Palomo or Kim.

ART RELIED UPON IN FINAL REJECTION

The listing of the references relied upon by the Examiner for the Final Rejection is correct as stated on page 3 of the Examiner's Answer.

ARGUMENT

Since each of the Grounds of Rejection to be reviewed on Appeal relies on one or more of the Depui '184, Depui 771 or WO '624, which are all substantially similar in their disclosures, as the primary reference, Groups 1 to 5 will be addressed collectively.

The Final Rejection is characterized by a number of deficiencies which renders the Final Rejection improper. The Examiner's Answer did nothing to remedy those deficiencies. The Final Rejection failed to employ proper standards, resorted to half quotes which, because they were incomplete, were misleading and other cited bits of information taken out of context without respect to consideration of the references as a whole. In some instances, the Examiner failed to cite to what she was actually referring to and often misstated the actual contents of patent disclosures. Also, neither the Final Rejection nor Examiner's Answer contained any authority for certain of statements regarding the standard of proof. Also, while Appellant had repeatedly requested compliance with 37 C.F.R. §1.104 to substantiate the statements made on the record, the Examiner did not in a single instance comply with the requirements of that rule.

A. THE FINAL REJECTION AND ANSWER FAILED TO COMPLY WITH 35 U.S.C. §103

The Primary References

Each of the rejections on appeal rely on one or more of Depui 184, Depui '771 or WO '624 as a primary reference. The Final Rejection and the Examiner's Answer continue to ignore that the invention of each of the Depui references and WO '624 is not a pellet but is a multi-unit tablet dosage form and each of the disclosures of the respective references is directed to their respective inventions. The pellets that Depui makes in either of the references are only one component of Depui's actual multi-unit tablet dosage form. As disclosed in each of the references, the pellets, after their preparation, are then added to a larger mass which contains microcrystalline cellulose, polyvinyl pyrrlodines, Naproxen® or a prokinetic agent, and other tablet excipients for a mixture and for introduction into a tableting machine to produce the final multi-unit tablet dosage form. The tablets are covered with a conventional tablet film coating layer. See Depui '771,

column 14, lines 55 to 63 and Depui '184, column 18, lines 34 to 59. Thus, it is clear that neither of the Depui dosage forms nor that of WO '624 are the same as the pharmaceutical preparation now claimed. Because the dosage forms are so radically different, the question of the chemical stability of the pellet *per se* is not a concern to Depui's invention or that of WO '624 because, in each instance, the pellet is further protected by more than the enteric coating and is only a component of the final dosage form.

The Examiner does not dispute that none of the examples in either of the Depui or WO '624 references produces a stable dosage form without a separating layer. The Examiner further does not dispute that the primary references fail to disclose how to obtain a stable pellet without a separating layer. Depui never states that his pellets are chemically stable by themselves. The Examiner cannot dispute that the dosage forms of the primary references are multi-unit tablets and are thus different from the dosage form contemplated by the presently claimed invention.

A fatal flaw of the Examiner's analysis of each of the primary references is her failure to consider the references as a whole and address this important difference. Rather, the Examiner repeatedly and erroneously asserted that the now claimed dosage form and those of the cited prior art were the same. The fatal flaw resulted from the Examiner failing to consider each of the references as a whole as is required under 35 USC §103. A review of the Final Rejection shows that in no instance did the Examiner acknowledge or mention the fact of the different dosage forms but merely repeated the error.

The comment at the top of page 20[2] of the Answer illustrates the Examiner's failure to appreciate, and include in her analysis, the difference between the pellets which are an

[2] The Answer states: The examiner points out that if the separating layer was absolutely critical to Depui's invention, the Depui would not insert the word "optional".

intermediate production in Depui and Depui's invention (and that of WO '624) and the dosage forms or inventions of these references. The question to be addressed is not whether Depui (or WO '624) considered a separating layer in a pellet as critical for the invention in those references but whether the Examiner can rely on only a portion of the disclosure of the primary references, ignore the remainder of the disclosure and in effect alter the prior art content and extrapolate comments concerning Depui's or WO '624's "invention" to only an intermediate portion thereof. It is submitted that this is not proper and at a minimum a failure to consider the art as a whole as required under 35 U.S.C. §103. One of ordinary skill would not, in view of other art, consider Depui or WO '624 as disclosing a chemically stable pellet of the acid labile compounds not having a separating layer.

Because the Examiner failed to consider the primary references as a whole, the Examiner erroneously asserted that Appellant's claimed invention and the primary reference dosage forms were the same. See Examiner's Answer at page 24, line 5 "The same dosage form is being claimed... ". Also see pp 32-33. Also see page 37, lines 9 to 10. This is manifest error and undermines the entire obviousness analysis conducted by the Examiner.

The Examiner also asserts that Depui's layer is same as Appellant's. Also see page 24, last three lines. This also is manifest error. There is no reason to believe that Depui's active layer and Appellant's substantially nonporous layer are the same. This is especially true since, as explained above, Depui's and WO '624's pellets are only a component of their respective multi-unit tablet final dosage form and, in the context of the entirety of those disclosures, there would be no need for any concern with respect to whether the pellet, as an independent unit, were stable. The stability issues of each of the Depui and WO '624 references are those that result from a mechanical problem, i.e., are mechanical stability issues. In fact, the Depui references distinguish

between the chemical stability issues and the mechanical stability problem. See for example Depui '771 starting at column 2, line 47 and continuing on to the top column 3, line 14 and in Depui '184 at column 2 at about line 42 and continuing on to column 3, at about line 8.

2. **The Term "Optional"**

The Examiner relied on the dictionary definition of the term "optional" rather than ascertaining the meaning of that term in the context of the Depui and WO '624 references. This is error and is an outgrowth of the Examiner not considering the art as a whole as required by 35 U.S.C. §103. The term "optional" cannot be viewed in a vacuum. Thus, one must recognize that the pellet referred to in the Depui references is not the final dosage form and will be mixed in to a formulation wherein the pellets are surrounded by a mass of material which, according to the examples in the Depui and WO '624 references, is greater than the total mass of the pellets. Thus, even if Depui's final dosage form included pellets without the separating layer, and Depui's final multi-unit tablet dosage form was stable, this would not suggest to one of ordinary skill in art that they would be able to make a stable pellet preparation of the benzimidazole active ingredients unless the pellet preparation itself contained a separating layer.\

What may be optional for the final multi-unit tablet dosage form of Depui was certainly not optional for the final dosage form of Lovgren as illustrated in his two U.S. patents attached to the Appeal Brief. Lovgren's dosage forms, which are more akin to those of the present invention but for the presence of the separating layer, are certainly different from those of Depui. In fact, as noted above and in the Appeal Brief, the Depui references refer to, and distinguish over, the '505 Lovgren Patent but only in connection with one portion of the structure and composition with which the Depui references are concerned.

3. The Final Rejection for Obviousness Improperly Relied on Inherency

The "Examiner's position" stated on the top of page 26 further illustrates that the improper way in which the Final Rejection has been constructed. With no authority or reason at all, the Examiner states that "the process would yield a similar result since the same type of machine is used". However, the Examiner has not denied that no where in any of the art cited by her is there a statement as to how to operate any of the apparatus be it a Wurster type fluidized bed or "similar equipment" to obtain a substantially non-porous layer. This failure of the prior art and the rejection, especially with respect to the Wurster type fluidized bed to describe proper conditions of operation to obtain a substantially non-porous layer on a pellet irreparably undermines the rejection.

As pointed out above, the presently claimed invention is to a method of preparing an oral pharmaceutical preparation with the features recited in the claims. The Examiner, without citation to any authority, indicates that proving lack of enablement of a prior art reference is high and asserts that because the prior art produced "a pellet", the prior art is enabled. However, the cited prior art does not produce just "a pellet" but a multi-unit tablet dosage form. But the rejection proceeds as if the cited prior art discloses and enables all or substantially all of the features of the now claimed invention. Thus, the Examiner has confused what a prior art reference must show to be enabling for the feature that the art supposedly shows. The pellets produced by Depui as intermediate parts may or may not be suitable whether they are stable or not for Depui's invention because those pellets are introduced into a larger mass and mixed therein to produce a final dosage form. The question is not whether Depui shows how to produce a pellet, but whether he shows how to produce a pellet without a separating layer which is a pharmaceutical preparation with sufficient chemical stability and not part of a tablet composition.

Contrary to the statement on page 34 of the Answer, the Examiner has not made a reasonable rationale to support her assertion that the active layer of Depui is substantially non-porous. In the composition of Depui, it would not matter whether the layer the Examiner is referring to is porous or not since that layer is further isolated from an aqueous or acidic environment by at least three additional layers thereon. Thus, there is no reasonable rationale because the Examiner has failed to comply with 35 U.S.C. §103 and consider the art as a whole. Accordingly, there is no *prima facie* case. It is only when there is a *prima facie* case that the Examiner can require a showing. Thus, the request for another showing on page 35 of the Answer is improper.

B. A TRANSITIONAL PHRASE CANNOT ALTER OR NEGATE RECITED CLAIM LIMITATIONS

The Examiner maintains that the term "comprising" is open ended and thus, the pending claims are open to the addition of a separating layer. Appellant repeats, and the Examiner does not deny, that the use of the term "comprising", does not authorize the Patent Office to ignore or alter the meaning of recited claim limitations.

Attention is invited to MPEP §608.01(o) at page 600-92 (8th Edition, Rev. 6) wherein the correct standard with respect to how the Patent and Trademark Office is to interpret claims for purposes of examination is set forth. Claims can be interpreted only as broadly as is reasonably supported by the specification. The Final Rejection fails to cite to the specification to support the erroneous interpretation of the claims allowing for the addition of a separating layer. Also, see *In re Hyatt,* 54 USPQ 2d 1664, 1667 (Fed. Cir. 2000) wherein the proper standard was repeated. The standard set forth in *Hyatt* was long ago adopted by the CCPA and obviously approved by the Federal Circuit. The MPEP at Section 2111 at page 2100-37 (8th Ed. Rev. 6) expressly states:

> During patent examination, the pending claims must be given their broadest reasonable interpretation consistent with the specification.

This standard was not cited by the Examiner nor was that standard applied in the Final Rejection. In fact, in the Answer, the Examiner denies this standard applies. See Answer at page 19. Once again, the proper standard for examination has not been followed. Use of the term "comprising" does not alter the standard for purposes of *ex parte* examination.

C. THE FINAL REJECTION DOES NOT CONTAIN LEGITIMIATE JUSTIFICATION FOR IGNORING THE DECLARATIONS

The submitted declarations were discussed on pages 21 to 25 of the Appeal Brief.

The Examiner does not deny that she has failed to comply with the standards for reconsideration of a showing as specified in *In re Piasecki* and *In re Rinehart*. Rather, the Final Rejection mainly avoids the submitted showings. As to each of the submitted showings, the Examiner has raised one or more theoretical speculations without documentary support, relegated each of the declarations to only addressing lack of enablement, asserted a high standard for showing lack of enablement and then concluded that the burden of disproving the unsupported speculations was on Appellant. This is a mere evasion to sidestep the mandates of *In re Piasecki* and is improper. Further, the Examiner has imposed an almost impossible burden to comply with during an *ex parte* examination. The Examiner has stated that "Appellant has not shown conclusively... ". See sentence bridging pp 36-37 of Answer. This is not the standard required for a submitted showing and further illustrates that the rejection was essentially set in concrete and Appellant's submissions were only considered, if considered at all, for their "knock down value". The proper standard requires the Examiner to step back from the rejection and evaluate the matter *ab initio* in view of the submissions and evidence contrary to the rejections. This was never done.

In the Answer, the Examiner at page 31 theorized that starch, which she states is a known disintegrant, affects the stability of certain tested dosage forms. A disintegrant does not cause instability of an active ingredient or render or change an otherwise stable dosage form into an unstable dosage form or change a compound from a stable compound to an acid labile substance. Disintegrants are used with tablets and for releasing tablets from a mold. It is the Examiner who has relied on primary references which are directed to forming a multi-unit tablet dosage. In fact, at page 15 of the Final Rejection, the Examiner describes the Depui disclosure as including use of binders, such as starches, in the reference formulation. Binders are not disintegrants. However, the Examiner did not raise the issue or refer to disintegrants or starches with respect to the submitted showing in the Final Rejection.

The Examiner criticized the Molina Declaration indicating that the formulations of Depui and the EP '797 are different. This is acknowledged on page 22 of the Answer. As explained on the record, the submission was in part to show that not all methods of producing coated pellets and not all methods of coating or types of coating apparatus can be used to obtain acceptable pellets. Also, Depui fails to provide practical guidance on the conditions of operation. Appellant therefore compared the otherwise closest prior art. See *In re Fouche*, 169 USPQ 429, 433 (CCPA 1971).

Again, on page 31, to avoid addressing the merits of the declarations, the Answer raises a theoretical issue that the excipients used in EP '787 might be causing instability. This had no support and was merely based on speculation. The Examiner then attempted to shift the burden to Appellant and called for another showing to then contradict the unsupported speculation. This is a blatant violation of the standard set down by *In re Piasecki*.

The attempt to relegate each of Appellant's showings to the enablement issue when in fact, the showings went to both issues of enablement and unexpected or improved results over the prior art was also error. For instance, the Examiner states that the declarations show that the prior art pellet is stable for an hour and this is sufficient for purposes of enablement. However, the Examiner ignores that the pellets of the present invention had improved stability and are stable for many months which would be an unexpected improvement over the prior art pellets with a chemical stability of an hour. However, this unexpected improvement was ignored in the obviousness analysis.[3]

The Examiner with no support at all asserted that "discoloration" may not necessarily result from degradation but from other causes. However, there is no basis in the record to support such a speculation. Once again, the Examiner raised an unsupported theoretical consideration with absolutely no supporting evidence or basis and then called upon Appellant to submit a showing to rebut the theoretical speculations. However, an Appellant need only submit a showing when a *prima facie* case has been made and, where there is no evidence to support an assertion by an Examiner, there can be no *prima facie* case. The Examiner required that Appellant's "conclusively demonstrate" that the resulting discoloration is due to instability rather than from other purposes. See for example the Answer at page 42. Thus, not only was there not a *prima facie* case that required a showing, but the Examiner demanded a level of proof far beyond what is reasonable even if there had been a *prima facie* case.

To prove lack of enablement, the Examiner required Appellant demonstrate that a pellet could not be made from the prior art. But the lack of enablement issue went to a pharmaceutical preparation of a pellet which did not have a separating layer but had sufficient chemical stability.

[3] As pointed out in the Appeal Brief at page 27, a claim need not recite the invention's unexpected advantages.

(See Answer at page 40). Appellant submits that this is strong evidence that the mandate of *In re Piasecki* was at least ignored if not intentionally avoided.

The Examiner also asserted that the showings were not commensurate in scope with the claims. However, it is well known from the art that this class of compounds is acid sensitive. In fact, it is known from the art that compounds which are considered "acid labile" must be protected from the acid environment of the stomach by a separating layer. See Lovgren's '230 Patent which has long been of record and was submitted with the Appeal Brief. The '230 Patent discloses a large number of acid-labile substances and refers to other references which disclose even other substances which are acid labile and which are protected from acidic environments only when a separating layer is used. Thus, there is information of record that provides a reasonable basis to expect Appellant would obtain the same results irrespective of the identity of the acid labile anti-ulcer active. Thus, no further comparisons were required and that submitted was sufficient in scope.

Another unsupported speculation appears on page 37 of the Answer, that it is that the material, rather than the structure, accounts for stability. However, a comparison of Tables 1, 2 and 3 of Lovgren's '505 Patent, also being of record, shows the error of this speculation. The '505 Patent, contains data showing that in Lovgren's formulation it is not a question of the material itself, but it is a question of the material and the location of the material structurally within the dosage form.

Table 1 of the '505 Patent shows the formulations for the core which contains hydroxypropyl cellulose (HPC). Table 2 shows the formulations for the coatings and shows in the separating layer of formulation II there is a content of HPC. Table 2 also shows that for coating formulation I, there is no separating layer. Table 3 compares the stabilizing effects based on

appearance of the preparation under certain specified conditions. It will be seen in almost every instance but one, those cores with coating preparation II were less discolored than those cores having coating layer preparation I but no separating layer even though HPC was also contained in the core subjected to coating preparation I. Thus, the Examiner's speculations are contradicted by the prior art and information of record. Appellant need not have submitted any further evidence on this point.

Contrary to the Examiner's protestations on page 38, the Final Rejection continuously intermingled enablement and a showing of unexpected results or improved results. This is not a question of the interest of compact prosecution being served, in fact this matter has been unduly prolonged. Declarations have been submitted, each of which should have been considered on both the lack of enablement issue of the prior art and the question of improved or unexpectedly improved results of the now claimed invention over the prior art. As explained above, the declarations were treated as if limited to the question of enablement and were subjected to some unspecified and unsupported high standard. Prior art of record showing the error of the rejections was ignored as well as prior art which showed that all of the compounds in this class of compounds behave similarly and there was no reason to believe that the improved benefits of the claimed invention, as already illustrated, would be any different in other comparisons using other acid labile anti-ulcer substances as the active ingredient.

D. THE FINAL REJECTION AND ANSWER IMPROPERLY ATTEMPTED TO MODIFY THE REFERENCE DISCLOSURES

On page 38, the Answer continues to misinterpret the Ohno reference. Ohno never states or suggests that there is no difference in principle between different types of machines used for coating. This was repeatedly called to the Examiner's attention and the misinterpretation was

merely repeated. The quoted Ohno disclosure merely indicates that one can use the same conditions in a coating apparatus for an aqueous system as were used for an organic solvent system. In fact, on page 39 of the Answer, the Examiner admits that she has modified Ohno's disclosure but erroneously asserts that this establishes a *prima facie* case of obviousness. Once again, based on a misinterpretation of prior art, the Examiner has called for a showing.

E. ONE CANNOT RELY ON INHERENCY TO SUPPORT AN OBVIOUSNESS REJECTION

On page 40, the Answer relies on inherency which is improper in an obviousness rejection. The Answer assets that the application example and Depui's Example 5 are "similar" and thus the layers must necessarily be non-porous in Depui's example. As pointed out above, this is unsupported, has no basis in fact or science, is a non-sequitur and does not constitute a *prima facie* case requiring a showing.

Just as with the Depui references, the Answer asserts that WO '624 "discloses the same layer as Appellant." Similarly, there is no support for the conclusion that the prior art active layer "must be substantially non-porous". The only apparent basis for this is the Examiner's statement that the term "substantially" is a broad term and since the prior art reference has similar components, the Examiner assumes that the prior art layer must therefore be non-porous. From that assumption that the prior art layer must be substantially non-porous, there is a leap to another unsupported assumption, i.e., that when the structure of the prior art is substantially identical to that of the claims, then the properties must be the same. Thus, the Final Rejection is based on an assumption built on another assumption where neither assumption has any support. Again, after improperly stacking one assumption on another, the Examiner attempts to shift the burden back to Appellant requiring Appellant to disprove these assumptions. This is improper since the Examiner

must establish a *prima facie* rejection before Appellant is required to come forth with a showing. A rejection primarily constructed of an assumption or compounded assumptions does not establish a *prima facie* rejection. See page 42 of the Answer.

The Answer, at pages 43 and 44, discusses the rejections of the claims based on a combination of three or more references. The Answer does not deny that the Palomo reference discloses use of an intermediate coating layer nor does the Answer deny that the Kim reference does not address or solve the problem of rapid degradation of the proton pump inhibitor compounds in an oral dosage form. The Answer asserts that each of these references is relied upon for a limited purpose and states that "Kim is not relied upon to teach the problems of rapid degradation of anti-ulcer compounds since this is not the premise of the rejection". This highlights a basic problem throughout this prosecution that a reference, once cited, was not considered in its entirety but rather treated only as if it had a limited disclosure which supported the rejection whereas the reference disclosure often, such as in the Lovgren '505 Patent, also contained disclosure which contradicted the rejection. That latter species of disclosure was ignored as if it didn't exist.

The Kim reference relates to omeprazole compositions designed for rectal administration. Thus, the dosage form addressed in Kim would not have to pass through the acidic environment of the stomach to arrive at the target parietal cells. Thus, the problems addressed by pharmaceutical preparation of the present invention are not encountered in the Kim dosage form. Accordingly, one of ordinary skill would not look to the Kim reference to solve problems encountered with a dosage form which is orally administered. The Kim dosage form, being administered rectally, would not be concerned with the particular problem of an orally administered composition would encounter. In fact, Kim's solution is simply to avoid having the

dosage form enter the highly acidic environment of the stomach. Thus, the conclusion at the bottom of page 43 of the Answer is erroneous where it states that the pellet's unexpected property providing a "stable pellet" is actually taught by Kim. Kim does not teach the pellet but does acknowledge the fact that compounds such as omeprazole undergo rapid decomposition in acidic environments and also refers to what was understood to be the proposed mechanism of action of the class of compounds by an acid catalyzed rearrangement.

In column 2, starting at about line 22, the Kim reference indicates that the pH in the rectum is in the range of 7.0, a weakly alkaline or neutral range but not an acidic range, and acknowledges that the object of the invention is obtained by using a different route of administration. Thus, it is not understood how one of ordinary skill would consider that Kim provides a chemically stable pellet for oral administration since Kim acknowledges the different pH environments encountered based on the method of administration.

F. THE COMBINATION OF REFERENCES IS IMPROPER

Throughout prosecution, Appellant urged that the combination of references was improper and no motivation was provided in the art to combine the references as had the Examiner. As discussed above, the references are different in terms of the end dosage form product, the structures utilized and the results obtained. There is no motivation to proceed as has the present Appellant and thus the combination of references is improper. Even if isolated parts of the invention were to exist in various references, that does not provide motivation to one of ordinary skill in the art to proceed as has the present Appellant. See *In re Grabiak*, 226 USPQ 870, 872 (Fed. Cir. 1985). Here no reference or combination of reference of record suggests or enables the now claimed invention. In fact, the art teaches away from the now claimed invention. See Lovgren '505 and '230.

CONCLUSION

In view of the foregoing, the Final Rejection should be reversed and claims 15, 16, 18-25, 30, 31, 33, 34, 36 and 39 to 50 should be allowed.

It is believed that no additional fees or charges are required at this time in connection with the present application. However, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,

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